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The Children's Oncology Group Radiation Oncology Discipline: 15 Years of Contribution to the Treatment of Childhood Cancer

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Abstract

Purpose: To review the advances in radiation therapy for the management of pediatric cancers made by the Children's Oncology Group (COG) radiation oncology discipline since its inception in 2000.

Methods and Materials: The various radiation oncology disease site leaders reviewed the contributions and advances in pediatric oncology made through the work of COG. They have presented outcomes of relevant studies and summarized current treatment policies developed by consensus from experts in the field.

Results: The indications and techniques for pediatric radiation therapy have evolved considerably over the years for virtually all pediatric tumor types, resulting in improved cure rates together with the potential for decreased treatment-related morbidity and mortality.

Conclusions: The COG radiation oncology discipline has made significant contributions towards the treatment of childhood cancer. Our discipline is committed to continuing research to refine and modernize the use of radiation therapy in current and future protocols with the goal of further improving the cure rates and quality of life of children stricken with cancer.

Introduction

The American Cancer Society estimates that 10,270 new childhood cancer cases and 1190 childhood cancer deaths are expected in 2017.[1] In 2000, four NCI-funded cooperative groups charged with studying childhood cancer [the Children's Cancer Group (CCG), the Pediatric Oncology Group (POG), the Intergroup Rhabdomyosarcoma Study Group (IRSG), and the National Wilms Tumor Study (NWTS)] merged to form the Children's Oncology Group (COG) – the largest cooperative group dedicated to the study of childhood cancer in the world. Due to the valuable contributions of these different cooperative groups and the excellent accrual of children on prospective national clinical protocols, childhood cancer mortality rates have declined by 66% and 5-year survival has increased from 58% in the past to 83% currently.[1] The radiation oncology discipline (including radiation oncologists and medical physicists) has always been an integral part of each of these constituent groups and its seamless assimilation into COG has facilitated the ongoing work of the group in designing, conducting, analyzing and reporting prospective multi-institutional clinical trials for the treatment of childhood cancer. Our discipline was led by Dr. Robert Marcus (2000–2005), Dr. Tom Merchant (2005–2015) and currently Dr. John Kalapurakal (2016 - present). On the occasion of completing the 15th anniversary of the formation of COG, we highlight some of the significant contributions of the radiation oncology discipline and the impact our specialty has made on the treatment of childhood cancer.

CNS Tumors

Medulloblastoma, ependymoma and glioma are common pediatric CNS tumors which require radiotherapy (RT) as part of their treatment.[2] Since 1970, the 5-year relative survival rates for children with CNS tumors have improved from 57% to 74%.[3] The COG has led clinical advances in radiation treatment planning and delivery, enabling the exposure of RT doses to smaller volumes with fewer side effects (table 1).

Radiotherapy, combined with surgery and chemotherapy is the cornerstone for the treatment of medulloblastoma. COG studies have been pivotal in delineating many specific treatment strategies that have improved clinical outcomes. Cranio-spinal irradiation (CSI) dose reduction from 36 Gy to 23.4 Gy in patients with average-risk disease yielded inferior event free survival (EFS) when delivered without chemotherapy[4] but equivalent EFS if given with concurrent and adjuvant chemotherapy (COG study A9961).[5] Compared to post-RT chemotherapy, neoadjuvant chemotherapy had no effect on 5-year EFS (POG study 9031).[6] The addition of involved-field RT to post-operative chemotherapy improved EFS in infants not receiving CSI (POG study 9934).[7] Lower dose CSI (18 Gy) with concurrent and adjuvant chemotherapy yielded inferior OS and EFS in children ages 3 to 7 years with average-risk medulloblastoma compared to higher doses (23.4 Gy), but reducing boost volumes from whole posterior-fossa to tumor bed plus margin did not compromise outcomes in average risk patients (COG study ACNS0331).[8] For high-risk medulloblastoma, giving carboplatin concurrently with CSI as a radiosensitizer was tolerable, and resulted in an encouraging 5-year EFS of 71% (CCG study 99701).[9] A trial evaluating concurrent carboplatin and isotretinoin with RT in high risk patients is currently ongoing (COG study ACNS0332). Current and future treatment paradigms incorporate molecular classification. The COG ACNS 1422 and the European SIOP PNET 5 protocols are evaluating 18 Gy CSI without concurrent chemotherapy for patients with WNT-driven non-metastatic medulloblastoma. For higher risk patients (M+ or poor molecular classification) radiosensitization or adjuvant therapy escalation is being considered.

The treatment paradigm for ependymoma consists of gross-total (GTR) or near-total resection (NTR) followed by post-operative RT. The first RT-inclusive COG ependymoma trial closed in 2007(COG study ACNS 0121).[10] Children with grade 2 supratentorial tumors with a microscopic GTR were observed, while those who had grade 3 tumors received immediate post-operative RT (54–59.4Gy). Children with posterior fossa tumors who underwent sub-total resection (STR) received two cycles of chemotherapy, possible second-look surgery and RT (54–59.4Gy). Children with posterior fossa tumors who underwent GTR or NTR received immediate post-operative RT (54–59.4Gy). This trial showed that 45% of patients observed after completely resected grade 2 supratentorial ependymoma recurred. Following NTR, cisplatin-based chemotherapy yielded a 40% complete response rate and may have facilitated second look surgery. However, when given to patients with <90% of their tumor resected, chemotherapy increased treatment-related toxicity and provided minimal clinical benefit.[11] STR best predicted 5-year EFS (61% vs. 39%), which validated similar benchmark institutional data (81% vs. 41%).[10] Immediate post-operative RT for resected posterior fossa ependymoma improved outcomes in children as young as 12 months, and a clinical target volume (CTV) expansion of 1.0 cm was adequate.[10] A follow-

up COG ependymoma trial ACNS 0831 is currently accruing which randomizes patients with complete or near-complete resection to adjuvant chemotherapy and uses a CTV margin of 0.5cm. In Europe, the SIOP-EP-II protocol also addresses the use of adjuvant chemotherapy in low risk patients in non-randomized patients. For high-risk patients the SIOP-EP II adds an 8 Gy stereotactic boost to residual disease and a randomized evaluation of the use of high dose methotrexate.

COG studies of supra-tentorial high-grade glioma (HGG) have shown improved survival with the addition of temozolomide and lomustine to standard-of-care RT compared to historical controls, with the greatest benefit seen in GBM patients with MGMT overexpression (COG study ACNS0423).[12,13] However, concurrent chemotherapy and RT in diffuse-infiltrating pontine gliomas (DIPG) has yielded little success (POG study 9836).[14] A study of the G2 checkpoint inhibitor AZD1175 given concurrently with RT in DIPG is ongoing (COG study ADVL1217).

For low grade gliomas, COG study ACNS 0221 protocol studied the efficacy of 54 Gy in unresectable tumors showing no response after at least one cycle of chemotherapy. CT. Reduced RT volumes with a CTV of 5mm were used. Data from this study and the European study SIOP-LGG-2004 for progressive low grade glioma are currently maturing and results are pending.

Rhabdomyosarcoma (RMS) and the Non-Rhabdomyosarcoma Soft Tissue Sarcomas (NR-STS)

The curative approach to soft tissue tumors of children began with the multi-disciplinary management of childhood RMS in the prospective IRSG protocols I-IV. Radiation oncologists have played an essential role in these studies paving the way for current COG studies. IRSG studies established the dose/volume standard guidelines of 50.4 Gy and 41.4 Gy for children with gross and microscopic disease respectively, emphasizing organ preservation, organ function, and quality of life.[15–22] (table 2).

Treatment for RMS is defined by risk of relapse. Low-risk RMS broadly includes favorable site, embryonal/botryoid histology, resected with/without microscopic disease, with specific subgroups having other features as defined by protocol. The D9602 and ARST0331 studies confirmed that patients with embryonal/botryoid histology with only microscopic disease can be effectively controlled with 36 Gy; those with resected lymph node disease N0/N1 with 41.4 Gy.[23,24] Patients with orbital primary tumors receiving modest cyclophosphamide doses have excellent 5 year FFS of 87%, and may be treated with 45 Gy, but those with less than a complete response to induction chemotherapy require 50.4 Gy.[25] Girls with vaginal RMS require RT by week 12 regardless of response to chemotherapy.[26]

Intermediate-risk RMS is defined as: non-metastatic patients with alveolar histology; embryonal histology not low risk; and embryonal patients <10 years with metastatic disease. Tumor size is prognostic, as shown in D9803. Patients with group III tumors <5 cm treated with 50.4 Gy have 10% local failure at 5 years, compared to 25% for tumors ≥5 cm.[27] Tumor site is also important, but even tumors of unfavorable sites can be controlled with RT,

e.g. hand/foot alveolar tumors have 100% local control at 10 years following RT confirming that amputation is not appropriate.[28]. The current COG intermediate risk RMS study (ARST1431) escalates RT dose to 59.4 Gy for tumors >5cm in size, and tests the addition of temsirolimus to the chemotherapy regimen. ARST1431 is also testing further refinements in RT that may help reduce late effects such as adaptive planning where only the post-chemotherapy volume is targeted after 36 Gy. The European cooperative groups are similarly testing dose escalation for tumors at highest risk of local failure. Current COG protocols provide guidelines for proton therapy and SBRT and the use of these advanced technologies is increasing rapidly. The COG will have a rich repository of dosimetric data available for future evaluation of outcomes with these modalities.

Timing of RT is not critical for most patients with intermediate-risk disease. Less than 2% of patients suffer local disease progression during induction chemotherapy.[29] Even patients with parameningeal tumors and features of intracranial disease, cranial nerve palsy, or skull base erosion can defer RT until after induction chemotherapy.[30] On the other hand, delayed RT (>24 weeks or omitted completely) is associated with local-regional recurrence, even in low-risk disease.[26]

High-risk/metastatic disease requires RT for local control of all sites that can be localized, though failure is often systemic. Recommended doses/volumes follow intermediate-risk guidelines.

Diagnostic cross sectional imaging (CT/MRI) and/or delayed surgery cannot reliably predict response but volumetric and metabolic response remain areas of active investigation for both the COG and European groups. However, RT cannot be omitted based upon imaging or pathologic response.[31,32] PET/CT can identify in-transit nodal spread.[33,34] Precision clinical staging is essential, with biopsy of regional nodes when possible, as nodal disease requires RT. Delayed primary excision has not obviated the need for local-regional RT nor impacted local control over RT alone.[35] Radiotherapy quality control is essential; local recurrence is associated with non-compliance with RT guidelines.[36] Chemotherapy alone is not sufficient local-regional therapy for RMS; patients with microscopic and gross disease profit from local-regional RT. The only children in whom RT is not routinely recommended are those with low-risk, completely resected disease.

In pediatric non-rhabdo soft tissue sarcoma the role of RT and chemo-RT has been defined by COG study ARST0332. Indications for RT are determined by: localized vs metastatic, surgically resected, margin status, grade, and size (figure 1). When delayed resection is planned, neoadjuvant chemo-RT with 45 Gy is used; microscopic positive margins receive 55.8 Gy, while macroscopic disease needs 64.8 Gy.[37] Certain histologic subtypes are chemo-responsive, thus chemo-RT combinations may be useful; other soft tissue sarcomas are successfully managed with RT and surgery alone. The recommended RT technique for all pediatric soft tissue sarcomas is highly conformal RT using image guidance, and either intensity-modulated or particle beam therapy.[38] Currently, the COG is conducting a prospective trial for non-rhabdo soft tissue sarcoma in partnership with the NRG cooperative group using a consistent treatment approach for both pediatric and adult patients.

Hodgkin Lymphoma

The COG Hodgkin Lymphoma (HL) committee continues to advance the treatment of children with HL by testing new treatment options aimed at improving cure rates while reducing treatment-related toxicity (table 3). The paradigm of response-adapted utilization was demonstrated to be an effective means of refining RT utilization in the COG AHOD0031 study. Selected patients with intermediate-risk HL who had a rapid and complete anatomic response to four cycles of dose-dense ABVE-PC chemotherapy did not have a significant improvement in event-free survival with the addition of adjuvant RT.[39] Detailed analysis of the study results further demonstrated that patients with a combination of the clinical features of mediastinal bulk and anemia had significantly better outcome with the addition of RT despite a rapid or complete response to chemotherapy, while those with multiple non-bulky sites did not benefit from RT.[40]

The management of high-risk HL remains a challenging problem, as the achievement of high cure rates has typically required treatment with significant doses of doxorubicin, alkylating agents and RT. The ongoing COG AHOD1331 trial evaluates the incorporation of brentuximab vedotin, a novel anti-CD 30 antibody-drug conjugate, into the upfront treatment of children with high risk HL. This agent, which has demonstrated remarkable clinical activity in the relapse setting, has the potential to substantially reduce the relapse rate in high-risk patients without the cumulative toxicity of additional conventional treatment. Further development of modern RT in this trial moves away from the large normal tissue volumes required to treat all initially involved nodal sites, and employs involved-site RT, limited to bulky mediastinal adenopathy and nodal areas not achieving a Deauville 3 response after two cycles of chemotherapy.

As COG trials continue to refine the selection of HL patients for RT, it is increasingly recognized that the risk-benefit considerations that drive management decisions are made largely based on studies such as the Childhood Cancer Survivor Study (CCSS) that examined the outcomes of treatments using outdated RT techniques. For example, COG investigators have demonstrated that for patients with stage I/II HL, the radiation dose to the heart and (female) breast tissue in the most recent COG trials are 69% and 84% of the doses received by CCSS subjects.[41] Given the linear dose-risk relationship described for many RT-related late effects,[42] these findings portend the anticipated reduction in late effects that are expected for survivors of COG trials. In addition, ongoing work continues to aid the refinement of treatment intensity by modeling the outcome of potential changes in RT utilization to provide a more quantitative and less speculative understanding of how to optimize the tradeoff between the risks of HL relapse and late toxicity.

Both COG and European trials are converging on the use or response-adapted involved-node RT for patients with early stage disease. The appropriate RT dose for patients with persistently PET-avid lesions following chemotherapy is an emerging issue that will require evaluation. European trials have focused on developing quantitative measures of PET-avidity and dose-intensification of chemotherapy as means of using RT more judiciously, whereas COG trials continue to use Deauville scoring of PET response, with substitution of conventional chemotherapy agents with novel agents. Ongoing efforts by COG HL

investigators are characterizing the biology of HL treatment response and prognosis. In addition, the routine collection of imaging datasets will facilitate the conduct of radiomic studies that will aid the evaluation of staging and treatment response. Collaborations are also underway with adult oncology trial groups to develop a joint trial for adolescents and young adults with unfavorable early-stage disease, and as a greater proportion of relapsed patients will be radiation-naïve there is increasing attention turning toward the appropriate dose for patients with chemotherapy resistant disease, and how to optimally incorporate RT into protocols for patients with relapsed HL.[43]

Ewing Sarcoma and Bone Tumors

Advances in chemotherapy combinations as well as improvements in surgical and RT techniques have led to continued improvement in outcomes for patients with localized Ewing sarcoma treated on COG studies (table 4). The addition of ifosfamide and etoposide (IE) to vincristine, doxorubicin and cyclophosphamide (VDC) improved both local control and overall survival while interval compression of VDC alternating with IE chemotherapy improved survival compared to standard 3-week dosing (COG study AEWS0031).[44,45] As therapy has improved for localized Ewing sarcoma, nearly 80% of patients are expected to be long-term survivors and functional outcomes are becoming increasingly important. The Ewing study committee has focused on utilizing advances in RT delivery as well as response-adapted therapy to reduce toxicity and improve local control. In the recently completed localized Ewing sarcoma COG study, AEWS1031, a provision for response-adapted post-operative RT as a method to reduce RT volumes for favorable responders was included to reduce risk of musculoskeletal complications after treatment. Specifically, for patients with microscopic positive margins after surgery requiring adjuvant RT, the RT target volume was based on response such that the post-chemotherapy, pre-operative volume was targeted in patients with good pathologic response (>90% necrosis), whereas the larger pre-chemotherapy volume was targeted for poor responders. CTV margins for RT were reduced from 1.5 cm to 1.0 cm with no apparent detriment to local control. In addition, AEWS1031 was the first trial from the COG Bone Tumor Disease Committee to systematically study surgical and RT techniques and volumes in relation to musculoskeletal complications. Although local control for primary tumors exceeds 90% on recent COG trials, local control for patients receiving definitive RT has stagnated at 80%.[46] Retrospective analysis of patients treated on the most recent completed COG trials suggest this is primarily due to poorer local control for older age patients (>18) and patients with pelvic tumors.[47] Recently presented data from the EuroEwing99 R2Loc study suggests that in high-risk patients (defined primarily as pathologic poor responders but some based on tumor volume >200mL) have improved survival with the addition of busulphan-melphalan (BuMel) high-dose chemotherapy with stem cell rescue (HDSCT).[48] The 3-yr EFS for the HDSCT cohort was 67%, compared to 53% in the standard arm. Five year EFS on the most recent COG study using interval-compressed chemotherapy was 73% and it is difficult to match the patient population to compare outcomes for the “high-risk” sub-set. However, surgical patients on COG studies have favorable outcomes and 80% of patients on the R2Loc study had surgery as a component of local therapy. In addition, because of concern of toxicity, central axis tumors were not eligible and pelvic patients had to defer radiotherapy until after high-dose

chemotherapy so caution should be taken with adopting this treatment strategy. The upcoming challenges for localized Ewing sarcoma include improving local control for patients with unresectable pelvic tumors and identifying a high-risk population that may benefit from more intensive chemotherapy such as the EuroEwing99 regimen. Analysis of EFS outcomes by size and PET and pathologic response on the recently completed AEWS1031 are currently underway to help answer these questions.

Although outcomes in patients with localized disease have improved over time, outcomes for patients with metastatic disease remain poor. In the recently reported EuroEwing99 R2Pulm, there was no benefit and increased toxicity for patients treated with BuMel compared to whole lung irradiation (WLI).[49] However, 3-yr EFS was over 50%, the best outcomes reported so far for patients with lung-only metastases, confirming the importance of whole-lung irradiation to consolidate patients with lung metastases. European and single institution data suggest that consolidation of all metastatic sites with RT improves EFS for patients with metastatic disease.[50] Stereotactic body radiotherapy (SBRT) is an emerging technique that can allow definitive dose RT to be administered in rapid time frame (1 to 5 fractions) and has been used to successfully treat sarcoma metastases in single institution trials.[51,52] To improve compliance with the recommendation for RT of all metastatic bony sites, the current metastatic COG Ewing trial, AEWS1221, allows SBRT given in 5 fractions, as opposed to the current standard of 31 fractions. By reducing treatment time and volume we will evaluate whether SBRT will improve compliance with RT to metastatic sites as well as examine local control outcomes with this newer technology.

Renal Tumors

The National Wilms Tumor Study (NWTS) conducted five clinical trials (1969–2002) that successfully reduced the indications for and doses of abdominal RT for children with Wilms tumor. Presently 75% of children with stage I and II tumors do not need RT, and the flank RT dose has been reduced from an age-adjusted regimen (18–40Gy) to just 10Gy for stage III tumors.[53] The COG renal tumor committee is the successor of the NWTS. The first generation of COG Wilms tumor (WT) protocols has just been completed (2003–2015) and data analysis is underway (table 5). COG study AREN0321 studied high risk renal tumors including diffuse anaplastic Wilms tumor (DAWT), malignant rhabdoid tumor (MRT) and clear cell sarcomas (CCSK). This study evaluated whether an intensive chemotherapy regimen with cyclophosphamide/ carboplatin/etoposide alternating with vincristine/ doxorubicin/cyclophosphamide improved survival in DAWT and MRT. The RT objectives included delivery of higher dose flank RT (20Gy) for stage III DAWT, the addition of flank RT (10Gy) to regimen DD4A chemotherapy (vincristine, dactinomycin, and doxorubicin) for stage I DAWT, and omission of RT for stage 1 CCSK. Preliminary results indicate that survival for stage II-IV DAWT is superior to NWTS results with a 4 year EFS of 85%, 74% and 46% for stage II, III and IV tumors respectively. Mortality due to treatment-related toxicity, however, was 4.5%.

COG study AREN0532 studied very low and standard risk favorable histology (FH) WT. Preliminary results show a 4-year EFS and OS of 90% and 100% respectively for 116 children <2 years old with small tumors, no loss of heterozygosity (LOH) at 1p and 16q, and

stage I or II disease after nephrectomy alone.[54] For stage I/II tumors with LOH at 1p and 16q, the 4-year EFS after DD4A chemotherapy was 84% compared to 75% with 2 drugs. Among 543 patients with FH stage III tumors without LOH at 1p and 16q the 4 year EFS and OS was 88% and 96% respectively after regimen DD4A and RT. Lymph node involvement was associated with inferior event free survival (83% vs. 95%).[55]

AREN0533 studied higher risk FHWT to determine if whole lung irradiation (WLI) can be omitted for stage IV tumors with rapid complete resolution of lung metastasis after 6 weeks of regimen DD4A chemotherapy. This study also augmented chemotherapy with regimen M (DD4A, plus cyclophosphamide and etoposide) and WLI for slow incomplete responders. Preliminary results indicate that among 296 patients with lung metastasis 105 (39%) had a complete response at week 6 to regimen DD4A and their 4-year EFS and OS was 78% and 95% respectively without WLI. This was non-significantly inferior to the 85% EFS after WLI and DD4A chemotherapy in NWTS-5.[56] Among the slow incomplete responders, the 3 year EFS and OS was 88% and 92% respectively after regimen M and WLI. These outcomes were significantly superior to the estimated event free survival of 75% with regimen DD4A and WLI.[57]

COG study AREN0534 studied children with bilateral WT. Patients were treated with induction chemotherapy, followed by surgery when possible, and RT based on pathologic findings. Survival data for 208 children shows a 4 year EFS and OS of 82% and 95% respectively compared to 61% and 80% respectively for similar patients on NWTS protocols. After induction chemotherapy, 84% had definitive surgery by 12 weeks and 39% of patients retained at least parts of both kidneys.[58]

The study committee is planning the next generation of WT studies. In addition to the known clinical, pathologic and molecular markers, gain of chromosome 1q will be used for risk stratification and treatment assignment.[59] Novel RT techniques such as IMRT for liver metastases and cardiac-sparing whole lung IMRT utilizing 4D simulation will be implemented for stage IV tumors.[60–62] SIOP, on the other hand, continues to use a pre-chemotherapy nephrectomy approach, with flank radiotherapy to a dose of 14.4 Gy reserved for Stage III intermediate-risk tumors and 25.2 Gy for Stage II to III high-risk diffuse anaplasia and Stage III high risk blastemal type Wilms tumor. In the upcoming UMBRELLA SIOP-RTSG 2016 protocol, AP/PA flank fields will not be routinely used; instead the GTV includes only the contact zone of pre-surgical tumor with a CTV anatomically confined expansion of 5 to 10 mm including the para-aortic lymph node chain in the case of lymph node involvement.[63]

Neuroblastoma

Significant contributions to the treatment of high-risk neuroblastoma have been made by COG radiation oncology (table 6). In the 1990s the CCG 3891 protocol utilized RT only for patients with post-operative gross residual disease, with 10 Gy for abdominal or mediastinal sites and 20 Gy for extra-abdominal sites. Children who were randomized to autologous bone marrow transplantation (ABMT) received an additional 10 Gy in the form of total body irradiation (TBI). Firm conclusions were difficult to draw as not all patients were uniformly

treated with RT; nonetheless, results indicated that in combination with RT to the primary tumor, the addition of 10 Gy of TBI with ABMT improved local control compared with chemotherapy without TBI, suggesting a dose–response relationship for local RT.[64]

COG study A3973 recommended uniform RT for all patients and showed that RT was an essential component of the multimodality regimen used for high-risk neuroblastoma. However, there was no benefit of extensive lymph node irradiation, irrespective of the extent of surgical resection preceding stem cell transplant.[65] In COG study A3973, 21.6 Gy was prescribed to the post-induction chemotherapy, pre-operative primary tumor volume regardless of extent of resection. This approach has become the standard of care for high-risk neuroblastoma.

The subsequent protocol, COG ANBL0532 showed that tandem myeloablative consolidation therapy improved survival in patients with high-risk neuroblastoma especially in the setting of post-consolidative immunotherapy.[66] ANBL0532 was also the first neuroblastoma randomized trial in which a RT-related question was posed as a primary objective. The study built on prior data suggesting a dose-response for incompletely resected primary neuroblastoma tumors, and determined whether boosting gross residual primary disease to a total dose of 36 Gy would improve the 3-year local control rate, compared to historical controls. Final results are pending.

COG study ABNL 09P1 was a phase 1 clinical trial evaluating the feasibility of treating high-risk neuroblastoma with I-131 MIBG. The trial closed to accrual in 2015 and preliminary analysis indicates that it is safe to utilize therapeutic I-131 MIBG during the induction phase of high-risk neuroblastoma treatment. Therapeutic I-131 MIBG therapy is an important component of the next randomized phase 3 high-risk neuroblastoma trial, COG study ANBL1531, a five-arm study including three randomized arms. Two of the randomized arms will assess the use of therapeutic I-131 MIBG to improve event-free survival in patients whose tumors have MIBG avidity. This study will open to accrual in the near future. When compared with previous high-risk neuroblastoma protocols there are many differences to the radiation oncology guidelines of ANBL1531 that include more stringent normal tissue constraints, requirement for including the entire vertebral body including the posterior elements within the CTV, and decreasing the CTV margin from 1.5 cm to 1 cm in these young children. Finally, metastatic sites that require RT will be numbered in accordance with the MIBG Curie diagnostic classification.[67] This will facilitate assessment of recurrence and aid in re-irradiation treatments.

Future aims of the radiation oncology committee include increasing the RT dose for metastatic disease still present after ASCT and utilizing SBRT for recurrent and metastatic disease.

There are significant differences between the COG approach to the treatment of high risk neuroblastoma and that of the European International Collaboration for Neuroblastoma Research (SIOPEN) approach. Metastatic sites that do not completely respond to induction chemotherapy are not routinely treated in Europe as they are in the United States. Furthermore, SIOPEN treats the primary tumor to 21 Gy in 14 fractions regardless of

residual disease after surgical resection (they do not boost to 36 Gy) In North America, under the auspices of the COG, the potential benefit of a boost to gross residual disease is being evaluated as a primary aim in ANBL0532.

Future aims of the COG neuroblastoma radiation oncology committee include evaluating the additive or cooperative effects of therapeutic I-131 MIBG with focal radiotherapy in regard to treatment efficacy and toxicity. This is challenging in the context of both optimal radio-therapeutic dosing to primary sites with residual disease after surgery and metastatic sites that do not completely respond to induction chemotherapy. Additionally, plans are being made to study the role of SBRT in the treatment of recurrent and metastatic disease.

Leukemia

Radiotherapy indications for leukemia have changed significantly over the past few decades, mainly in the direction of reducing the intensity and/or indications based on risk-adapted therapy principles. The risks groups were established based on well-defined criteria validated in multiple clinical trials (Table 7).[68,69] COG studies have been instrumental in defining RT indications for newly diagnosed high risk pre-B cell ALL and T-cell acute lymphoblastic leukemia (ALL). Current guidelines for these patients include cranial radiation therapy (CRT) as part of CNS-directed therapy and treating residual disease in testes.[70,71] For relapsed disease, RT plays a role for isolated CNS relapses, as well as a conditioning regimen for stem cell transplant delivered as TBI with or without CRT and testicular boost based on specific risk stratifications defined by protocols.[72–74] Radiotherapy indications incorporated into recently completed and currently opened COG trials are listed in Table 8. COG RT guidelines emphasize precise integration of radiation into treatment road-maps with particular attention to be paid to its timing with concurrent systemic chemotherapy, as well as evaluation and management of patients' clinical condition, including concurrent and evolving toxicities. Late effects from cranial RT, testicular RT, and TBI can adversely affect the quality of life and survival of children treated for leukemia and are being evaluated in several ongoing prospective trials.[75]

Efforts in COG and other international pediatric cooperative groups continue to focus on reducing treatment-related side effects in this highly curable cancer. The cooperative group BFM (Berlin-Frankfurt-Múnster) is an important international platform for promoting research and clinical care for leukemia and lymphoma in children and adolescents in Europe and beyond. The BFM has taken a similar approach to the COG with the elimination of prophylactic CRT in patients with low-risk ALL and the successful stepwise reduction in CRT to 12 Gy in those with intermediate- and high risk ALL.[76]

Rare Tumors

The COG rare tumors committee has focused on improving outcomes for children with uncommon tumors that by nature require study in a cooperative group setting. For children with retinoblastoma the main focus has been to minimize exposure to radiation therapy in these vulnerable children. In early, stage I, disease COG study ARET12P1 uses intra-arterial therapy, eliminating external beam RT in the up-front setting and incorporating

brachytherapy when appropriate. This study recently closed and results will be forthcoming. For eyes that are Stage II or III, the COG ARET0321 trial prescribed multi-agent chemotherapy and 45 Gy RT. For Stage IV disease, chemotherapy and response-based RT was given, followed by ABMT. The EFS for stage 2 and 3 patients was 88% at 3 years and 79% for children with non-CNS metastatic disease.[77] These results are significantly improved compared to historical controls.

Nasopharyngeal carcinoma is another rare tumor where RT plays a major role. COG recently completed a prospective trial of response-based RT (COG study ARAR0331) with a goal of delivering lower (61.2 Gy) RT dose for the majority of patients. This trial enrolled 111 patients achieving a 5-yr. EFS of 86%.[78] Future studies will continue to refine the intensity of therapy required for chemotherapy-responsive patients.

Late Effects

Despite the remarkable success in improving survival in pediatric oncology, both RT and chemotherapy can cause debilitating or even fatal late effects that are critical to understand, mitigate, or prevent.[79,80] The Late Effects radiation oncology subcommittee has contributed to improving the outcomes of pediatric cancer patients in a number of ways. Its function includes (1) review of existing normal tissue RT dose constraints in COG protocols, (2) generating new evidence-based dose constraints for future COG protocols, (3) interfacing with the COG Late Effects Survivorship Guidelines committee for refinement of surveillance recommendations (http://www.survivorshipguidelines.org/), (4) identifying knowledge gaps relating to radiation-associated and combined modality normal tissue toxicities, and (5) training young investigators in RT late effects. The subcommittee has integrated with PENTEC (*Pediatric Normal Tissue Effects in the Clinic*) to form 18 organ-specific task forces led by COG radiation oncologists. This group will identify RT-associated normal tissue damage as a function of patient age at the time RT was delivered, dose (including parameters such as fraction size), volume, functional organization of the organ exposed, and the impact of ancillary cytotoxic therapy, primarily chemotherapy. The results of these investigations will provide clinicians with the best available data on which to make decisions in treating children for cancer with RT, and inform scientists on necessary future directions for research.[81]

Quality Assurance and Physics

The Imaging and Radiation Oncology Core (IROC) services at IROC Houston (formerly RPC) and IROC Rhode Island Quality Assurance (formerly QARC) Centers are responsible for providing RT and imaging quality assurance (QA) core support for the COG. Investigators from IROC have been involved with pediatric clinical trials since the origin of both the POG and the CCSG and continue to be part of the quality assurance mission of the COG. IROC works with each study investigator to write protocol guidelines that meet both study objectives and processes established by the NIH, and recommend appropriate credentialing and data management strategies for each study to insure that the goals of the study can be met with the highest quality data possible. IROC Houston is responsible for site qualification and credentialing institutions for participation in clinical trials that use

advanced technology RT including all facets of, and maintaining the list of participant institutions and their credentialing status. IROC Rhode Island is responsible for data acquisition, data management and pre and post case review for both imaging and RT objects required for each individual protocol.

The importance of the QA process in maximizing protocol compliance was demonstrated for the conduct of the COG AHOD0031 Hodgkin study mentioned previously. Rapid early review of RT treatment plans by IROC with remedial modifications made when necessary resulted in significantly fewer protocol violations as compared to retrospectively reviewed plans (figure 2).[82]

Perhaps the most significant technical advance in the last decade affecting the QA review of imaging and RT data is the evolution from hardcopy to exclusively digital formats. COG institutions currently submit digital data using a secure FTP site. This is now being transitioned to the American College of Radiology's Transmission of Imaging and Data (TRIAD) system. The development of digital media transmission tools has permitted real time (same day) evaluation of imaging and RT objects by the QA centers with ad hoc participation by site and study investigators as needed on a simultaneous basis. This evaluation capability has significantly changed protocol development as real time review of objects has permitted secondary and tertiary randomized RT objectives to be imbedded into studies. IROC continues to play an integral role in protocol core support for COG and will continue to be an important component in the success of each clinical trial.

The Physics Subcommittee has made significant contributions to the conduct and quality of RT in COG studies. A survey of portal imaging practices resulted in specific recommendations to reduce imaging radiation doses for pediatric RT.[83] A follow-up survey is currently underway. The Physics subcommittee will also review current RT practices in TBI and proton therapy on COG protocols.

Proton Therapy

General consensus has grown within the radiation oncology community that proton therapy can reduce acute and late toxicities in many clinical scenarios of childhood cancer compared to x-ray-based technologies. Objective data demonstrating these benefits are beginning to accrue.[84] Improved side effect profiles and quality of life outcomes have been reported for neurocognitive, hearing, and neuro-endocrine function as well as other arenas including second malignancy and acute toxicities.[85–94] Furthermore, cost effectiveness studies have found that proton therapy, despite upfront high cost, is cost-effective in the long run when expenses associated with side effect management are factored in.[95] COG radiation oncologists and proton physicists have developed specific guidelines for proton RT that are incorporated into COG protocol guidelines and have helped standardize the use of this modality for all tumors in a cooperative group setting. Currently there are approximately 21 proton centers across the country that have been approved by IROC to treat children on COG trials. Thus, COG studies are ideally positioned to help define the role and relative benefits of proton therapy in comparison to photon radiation based on prospective clinical data.

Pediatric Radiation Oncology Education and International Collaboration

COG seeks to improve pediatric radiation oncology education and training in North America and around the world, especially in low and middle income countries. The COG Radiation Oncology Committee includes 300 radiation oncologists and physicists (figure 3) and has an active Young Investigator program. As part of its mission, the committee provides training in state-of-the-art pediatric RT to both established and new pediatric radiation oncologists via dedicated educational sessions, seminars, and on-line resources. An international outreach program has also been established through collaborations with the Pediatric Radiation Oncology Society (PROS) and the International Society of Pediatric Oncology (SIOP). In this regard, a free COG educational platform has been created on the IROC-Rhode Island website (http://www.irocri.qarc.org/). Disease leaders from our discipline also moderate an online discussion forum (https://pediatric-oncology.chartrounds.com/) that aims to improve the quality of childhood cancer care globally through free and timely online discussion of cases with our experts. Such international collaboration facilitates exchange of ideas and helps develop clinical and basic research protocols that will benefit our field in the future.

Conclusions and Future Plans – Integration of Tumor Biology and Diagnostic Imaging into the Practice of Radiation Oncology

Since its inception 15 years ago the radiation oncology discipline of COG has made many noteworthy contributions aimed at refining the treatment of low-risk patients to decrease treatment-related toxicity and intensifying treatment of high-risk tumors to improve outcomes. We have consistently adopted measures to systematically reduce the radiation exposure of children by: 1) reducing the RT indications for favorable risk tumors (*Hodgkin lymphoma, Wilms tumor, CNS tumors, leukemia, retinoblastoma*), 2) decreasing the volume of normal tissues irradiated (*medulloblastoma, ependymoma, germ cell tumors, Hodgkin lymphoma, rhabdomyosarcoma, Ewing sarcoma, use of proton therapy and IMRT*) and 3) reducing the total RT doses for favorable risk tumors (*rhabdomyosarcoma, soft tissue sarcoma, medulloblastoma, Wilms tumor)* that will reduce late toxicity and enhance the quality of life of childhood cancer survivors. For higher risk tumors we have used higher RT doses together with intensive multi-agent chemotherapy regimens *(neuroblastoma, diffuse anaplastic Wilms tumor, rhabdomyosarcoma, Ewing sarcoma)* that will hopefully improve tumor control rates.

An inherent difficulty that clinicians face in making treatment decisions regarding any uncommon tumor (which includes most pediatric cancers) is the relative lack of data regarding various treatment approaches, and the slow pace at which new treatment techniques and paradigms can be tested and reported. Given these limitations, clinicians are often tempted to adopt treatment guidelines from ongoing prospective clinical studies as “standard of care” when treating children “off-study”. However, we urge caution when applying untested treatment approaches (e.g., radiation dose reductions or escalation, or changes in radiotherapy treatment volumes or target margins) that are study aims of ongoing investigational trials.

Future work in our discipline will continue to pursue novel ways to enhance the curative potential and reduce the adverse effects of RT. Studies by several groups including the Pediatric Preclinical Testing Program (PPTC) have shown the ability of using mouse models of pediatric cancer to identify novel effective drugs.[96,97] However studies of the efficacy of RT alone or in combination with potential radiation sensitizers have lagged behind. It is well-recognized that RT damage to DNA can be repaired by a plethora of enzymatic activities that lead to tumor cell survival or mechanisms that suppress death programs and ultimately resistance.[98] Importantly, specific and potent inhibitors of many DNA damage response pathways or small molecules that activate p53-induced apoptotic signaling are in preclinical development, or are under clinical evaluation for treatment of adult malignancies. However, translating these advances to the treatment of childhood cancer presents challenges. Preclinical models that accurately recapitulate the genetics and microenvironment of pediatric cancers may be used to identify those RT/drug combinations that have impact against a majority of models of specific histotypes, or more general broad potentiation of RT effects. Further, with advanced technologies such as nano-formulation, more selective tumor-specific radiation enhancement may be achieved. The use of appropriate preclinical animal models may be able to identify those combinations worthy of advancement to clinical trials and COG radiation oncologists are partnering with basic scientists to identify and translate these treatments into the clinical setting.

Additional areas planned for study include closer collaboration with diagnostic radiology to study the value of imaging modalities such as PET and novel MRI techniques to refine the indications and target volumes for RT, and treatment outcomes of various tumors *(Hodgkin lymphoma, rhabdomyosarcomas, Ewing Sarcomas, gliomas, and Wilms tumor)*. We will also study the potential differences between protons and photons on the brainstem by analyzing post-treatment MRI studies of children with ependymoma and medulloblastoma treated on COG protocols. Thus, the COG radiation oncology discipline is committed to continuing research with a broad range of disciplines to both refine and modernize the use of RT in current and future multidisciplinary protocols with the goal of further improving the cure rates and quality of life of children stricken with cancer.

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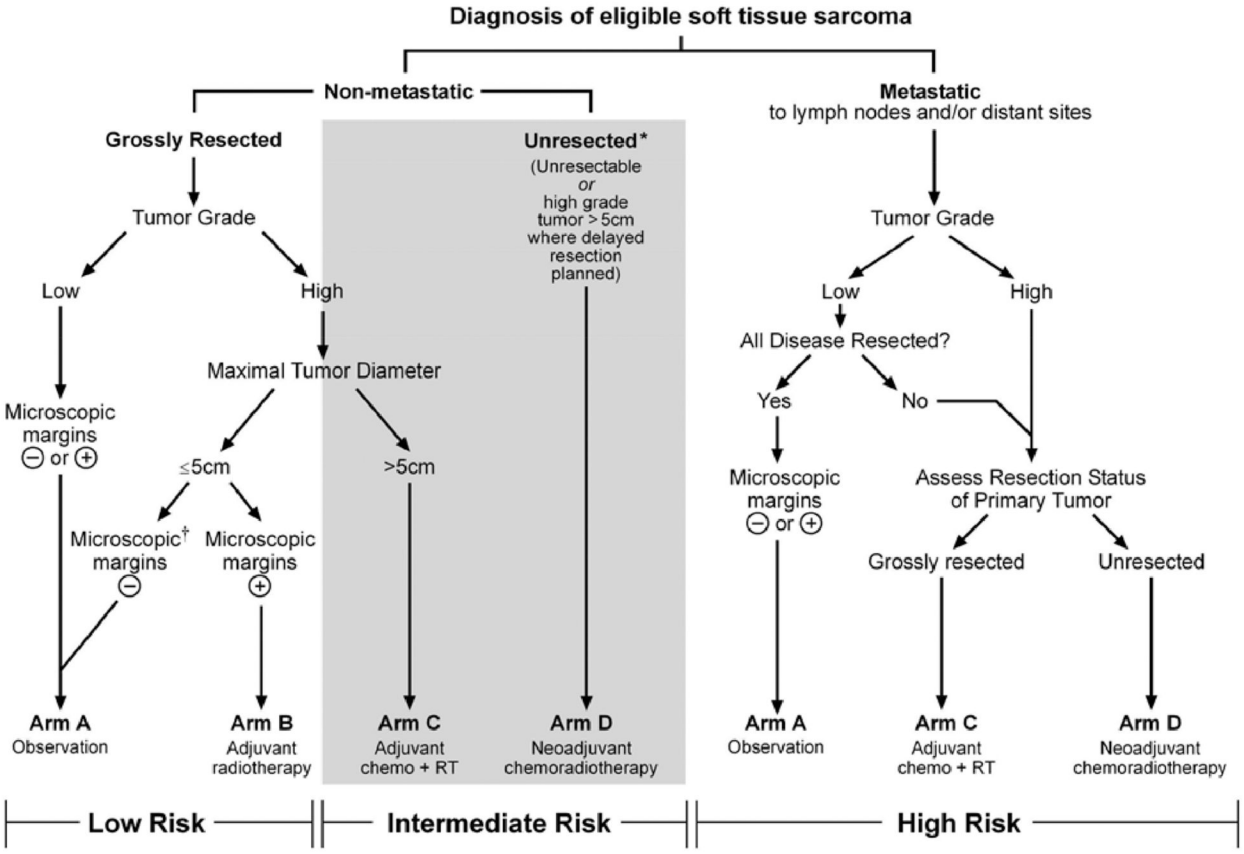

Figure 1:

ARST0332 guidelines for treatment of non-rhabdomyosarcoma soft tissue sarcomas. Management of these tumors is determined by extent of disease, grade, size, and margin status.

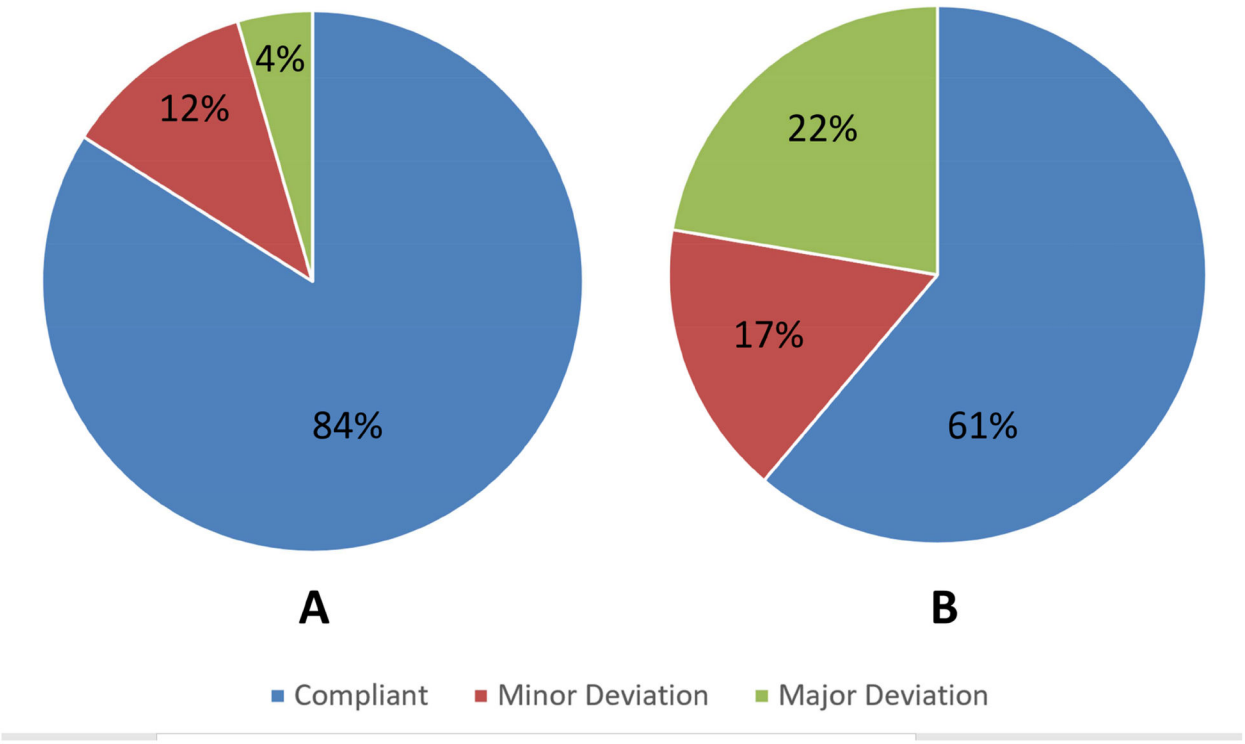

Figure 2:
Radiotherapy protocol compliance for AHOD0031. A: Compliance after central rapid review and remediation. B: Compliance in the absence of rapid review.

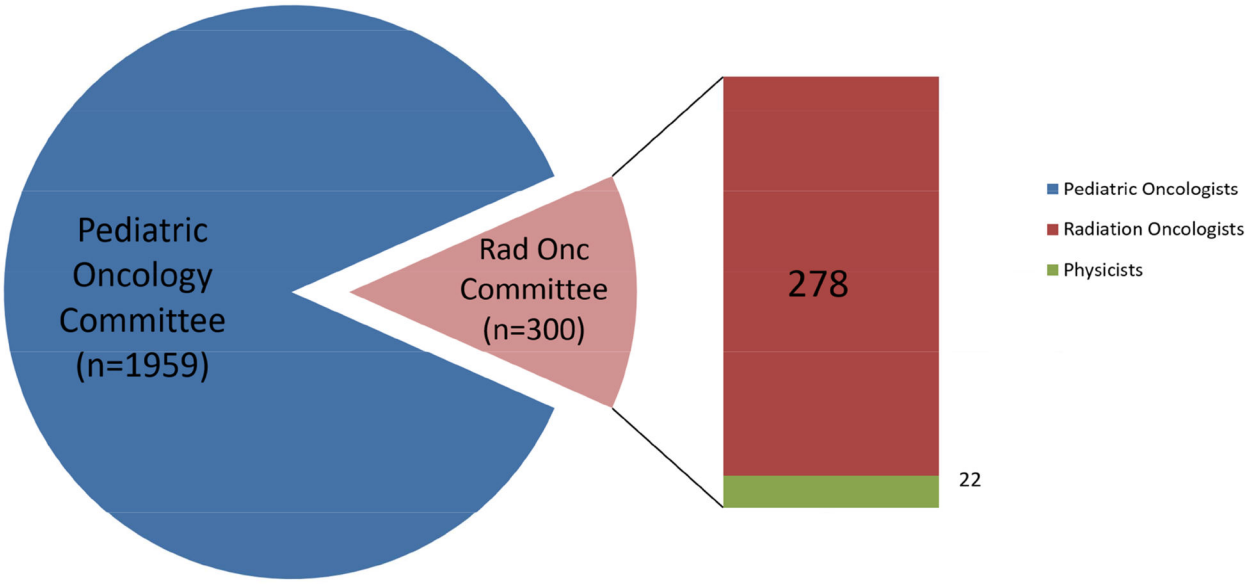

Figure 3:
COG membership breakdown. Radiation oncology committee members comprise 15% of the COG membership.

Table 1:

Major radiotherapy advancements in pediatric CNS tumors

• Reduced dose cranio-spinal RT (23.4 Gy) can be used for average-risk medulloblastoma if combined with adjuvant chemotherapy, but further decrease of CSI dose to 18 Gy results in inferior survival
• The addition of posterior fossa RT to chemotherapy improves survival in children less than 3 years of age with medulloblastoma, compared to chemotherapy alone
• In average-risk medulloblastoma, boosting “tumor bed plus a margin” has equivalent outcomes to boosting the entire posterior fossa
• For children with ependymoma, optimal treatment is gross total resection followed by immediate RT
• Concurrent RT and temozolomide followed by adjuvant temozolomide and lomustine for high grade gliomas improves survival compared to historical controls
• The safety and efficacy of proton therapy is being studied in prospective clinical trials

Table 2:

Major radiotherapy advancements in pediatric rhabdomyosarcoma

• Chemotherapy alone does not provide adequate local control for microscopic or gross residual rhabdomyosarcoma
• Microscopic rhabdomyosarcoma can be controlled with a dose of 36 Gy
• Rhabdomyosarcoma >5cm in size has a high local failure rate when treated with 50.4 Gy, and may require higher radiation doses for control
• Delaying RT for rhabdomyosarcoma beyond week 24 results in high local failure rates, but there is no advantage to early (prior to week 12) RT – even for parameningeal primary sites
• The safety and efficacy of proton therapy is being studied in prospective clinical trials

Table 3:

Major radiotherapy advancements in pediatric Hodgkin lymphoma

• RT can be omitted for most patients who have a complete anatomic response to chemotherapy
• Children with bulky mediastinal tumor and anemia had improved outcomes with adjuvant RT regardless of their response to chemotherapy
• Modern RT techniques as used in COG trials deliver significantly less radiation to normal tissues (for example, heart and female breast) as compared to older techniques that have been associated with treatment-induced morbidity
• The safety and efficacy of IMRT and proton therapy is being studied in prospective clinical trials

Table 4:

Major radiotherapy advancements in Ewing Sarcoma

• The addition of ifosfamide and etoposide (IE) to vincristine, doxorubicin and cyclophosphamide (VDC) improved both local control and overall survival while interval compression of VDC alternating with IE chemotherapy improved survival.
• In AEWS1031, a provision for response-adapted post-operative RT as a method to reduce RT volumes for favorable responders was included to reduce risk of musculoskeletal complications after treatment.
• Identification of older age (>18 years) and pelvic primary site as predictors of inferior local control for patients treated primarily with radiotherapy.
• The current metastatic COG Ewing trial, AEWS1221, allows SBRT to metastatic lesions given in 5 fractions, as opposed to the current standard of 31 fractions.

Table 5:

Major radiotherapy advancements in pediatric renal tumors

• Intensified RT and chemotherapy improves survival for high-risk renal tumors
• Tumor rupture was upstaged to stage III and flank RT was recommended
• Whole lung RT can be safely omitted for stage IV favorable histology Wilms tumor with lung-only metastases and without LOH at 1p and 16q, who have a complete response to DD4A chemotherapy
• Whole lung RT with regimen M chemotherapy resulted in excellent survival for stage IV favorable histology Wilms tumor with had slow incomplete response to DD4A chemotherapy
• For patients with bilateral Wilms tumor, induction chemotherapy, timely surgical resection and response-based RT results in improved survival
• Cardiac sparing whole lung IMRT and liver IMRT with 4D simulation and central QA review will be studied in prospective clinical trials

Table 6:

Major radiotherapy advancements in neuroblastoma

• Extensive lymph node irradiation is not required for patients with high risk neuroblastoma undergoing stem cell transplant
• Therapeutic I-131 MIBG can be safely administered to patients with metastatic neuroblastoma
• CTV margin for treatment of the primary tumor and metastatic lesions can be reduced from 1.5 cm to 1.0 cm.

Table 7.

ALL Risk Groups

Standard Risk: **All** of the following

- Age 1–10 years
- WBC < 50,000/mm3
- B-cell phenotype
- No or very few leukemia cells in spinal fluid
- No VHR features

High Risk: **Any** of the following

- Age ≥ 10 years
- WBC > 50,000/mm3
- T-cell phenotype
- Spinal fluid with ≥ 5 WBC/hpf and detectable lymphoblasts

And: No VHR features

Very High Risk: Any of the following

- High MRD at end of induction
- Adverse cytogenetics
  - MLL gene rearrangement
  - Hypodiploidy

Table 8:

Radiotherapy in COG leukemia trials

B-ALL High-risk:
CNS 3: CRT 18 Gy **(AALL1131)**
T-ALL:
Intermediate and High risk
CNS 1 and 2: CRT 12 Gy **(AALL0434)**
CNS 3: CRT 18Gy **(AALL0434; AALL1231)**
Very High risk ALL
CNS 1 and 2: CRT 12 Gy **(AALL0434)**
CNS 3: CRT 18 Gy **(AALL0434; AALL1231)**
Relapses:
Isolated CNS relapse after> 18 mo from diagnosis:
CRT 12 Gy **(AALL02P2)**
CRT 18 Gy for CNS 3 **(AALL1331)**
Early isolated CNS relapse<18 mo from diagnosis (AALL0433): CRT 18 Gy
Testicular Radiation:
Patients with continued evidence of testicular leukemia at the end of Induction:
Testicular RT to 24 Gy **(AALL1131; AALL1331)**
Conditioning regimen for hematopoietic stem cell transplantation: (AALL1331)
TBI 12–13.2 Gy
Cranial boost 4–6 Gy for CNS 3 disease
Testicular boost 6 Gy for persistent disease

CNS1 = no blast cells in CSF, CNS2 = <5 WBC/microliter CSF with blast cells, CNS3 = ≥5 WBC/microliter CSF with blast cells, or signs of CNS involvement